REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action, **a Final Rejection**, with appreciation. Claims 12-24 are pending in the application. The previous rejections under 35 USC § 112, first and second paragraphs, have been withdrawn in view of the Response and Amendment filed on February 5, 2009. The Office maintains a rejection under 35 USC § 103.

Claims 12-24 remain rejected for obviousness under 35 USC § 103(a) based on the disclosure of Ogletree, et al. (US Published Application No. 2003/0109543) in view of Lavielle, et al. (US Patent No. 5,472,979). The Office states that the rejection is maintained for the reasons of record. In the previous Office Action, the Office stated that Ogletree, et al. disclose compositions comprising an ADP-receptor blocking antiplatelet drug, such as clopidogrel, in combination with a thromboxane A_2 receptor antagonist, such as ifetroban, as well as a method for inhibiting platelet aggregation and thrombus formation by administering the disclosed combinations. The Office further stated that Ogletree, et al. disclose treatment of cardiovascular diseases with the disclosed combinations. The Office acknowledged that Ogletree, et al. do not disclose compositions comprising the instant compound (A) of formula (I).

With respect to the Lavielle, et al. reference, the Office stated that this reference discloses that the instant compound (A) of formula (I) is an anti-thromboxane A_2 receptor antagonist which is useful as an anti-thrombotic in the treatment of cardiovascular diseases.

The Office concluded that, based on the disclosure of Lavielle, et al. one skilled in the art would have been motivated to replace the thromboxane A_2 receptor antagonist, such as ifetroban, of the Ogletree, et al. composition with compound (A) of formula (I) to arrive at the instantly claimed combination.

With respect to the LEROND Declaration submitted with the Response and Amendment of February 5, 2009, it is the position of the Office that the comparative

data provided in the Declaration are not a sufficient demonstration of the superior/unexpected effects associated with the instantly claimed combination.

It is the position of the Office that, although the LEROND Declaration provides data demonstrating that synergy is observed with a combination of clopidogrel and compound (A) and that such synergy is not observed with a combination of clopidogrel and the thromboxane A_2 receptor antagonist BAYu3405, the Lavielle, et al. reference expressly teaches "a negative piece of information" with respect to the use of BAYu3405 for inhibiting platelet aggregation. The Office states that the Lavielle, et al. reference discloses that compounds of formula (I) exhibit "markedly more intense pharmacological activities" compared to reference compound BAYu3405. It is the position of the Office that, in view of this disclosure, one skilled in the art would not have contemplated combining BAYu3405 and clopidogrel for "testing out their synergy."

The Office goes on to state that Ogletree, et al. expressly describe a composition based on an ADP-receptor inhibitor, such as clopidogrel, and a thromboxane A_2 receptor antagonist for the treatment of cardiovascular diseases and that Lavielle, et al. disclose that the compound of formula (I) has "markedly more intense pharmacological activities" than BAYu3405. Therefore, the Office concludes that one skilled in the art would have been motivated to employ the compound disclosed in Lavielle, et al. as an alternative to BAYu3405 with a reasonable expectation of success.

The Applicants respectfully submit that the Office allegation that Lavielle, et al. teach a "negative piece of information" regarding the use of BAYu3405 for inhibiting platelet aggregation is not accurate. Although the Lavielle, et al. reference discloses that compounds of formula (I) exhibit activity equal to or greater than reference compound BAYu3405, this reference does not teach that BAYu3405 lacks efficacy in terms of inhibiting platelet aggregation, as suggested by the Office. Moreover, as noted in the LEROND Declaration, BAYu3405 is a marketed thromboxane A_2 antagonist.

The Applicants further submit that, although Lavielle, et al. teaches that the compounds of formula (I) exhibit platelet aggregation activity equal to or greater than the reference compound BAYu3405, one skilled in the art would not have expected a combination of clopidogrel and compound (A) to exhibit ***synergistic*** effects based on this disclosure. As demonstrated by the LEROND Declaration, the composition comprising clopidogrel and compound (A) exhibits activity which is not only superior to the composition comprising clopidogrel and BAYu3405 but also exhibits synergistic effects which are not observed with the composition comprising clopidogrel and BAYu3405.

Specifically, the previously submitted LEROND Declaration discloses comparative data in a thrombosis model for combinations comprising BAYu3405 and clopidogrel and compound (A) and clopidogrel as well as data for clopidogrel, BAYu3405, and compound (A) alone.

The data disclosed at pages 5-6 of the LEROND Declaration demonstrate the following:

> administration of clopidogrel alone increases time to occlusion by 2.1 min (an increase of 38% compared to control) and decreases the number of CFRs by 2.4/60 min (a decrease of 21% compared to control);
>
> administration of BAYu3405 alone increases time to occlusion by 2.3 min (an increase of 42% compared to control) and decreases the number of CFRs by 4/60 min (a decrease of 36% compared to control);
>
> administration of compound (A) alone increases time to occlusion by 3.7 min (an increase of 67% compared to control) and decreases the number of CFRs by 2.4/60 min (a decrease of 21% compared to control);
>
> administration of a combination of BAYu3405 and clopidogrel increases time to occlusion by 4.2 min (an increase of 76% compared to control) and

decreases the number of CFRs by 4/60 min (a decrease of 36% compared to control); and

administration of a combination of compound (A) and clopidogrel increases time to occlusion by 6.5 min (an increase of 118% compared to control) and decreases the number of CFRs by 7/60 min (a decrease of 63% compared to control);

These data demonstrate a lack of synergistic activity between BAYu3405 and clopidogrel. Moreover, these data also demonstrate the synergistic effects of the combination comprising compound (A) and clopidogrel, which synergistic effects are especially apparent by the decrease in the number of CFRs observed with the combination of compound (A) and clopidogrel as compared to monotherapy with either component.

The Applicants respectfully reiterate that the synergistic effects associated with the instantly claimed combination would not have been predicted based on the disclosure of the Lavielle, et al. reference related to the activity of compound (A) as compared to BAYu3405.

Thus, the Applicants respectfully submit that the superior and unexpected effects associated with the instantly claimed compositions are not taught or suggested by the Ogletree, et al. reference in combination with the Lavielle, et al. reference, and that, therefore, the combined disclosure of the cited references does not render the instantly claimed compositions, or the use of such compositions, obvious. Reconsideration and withdrawal of the obviousness rejection under 35 USC § 103(a) is respectfully requested.

* * * * *

Accordingly, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned agent has made an earnest effort to place this application into condition for immediate allowance. If she can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call her at her below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

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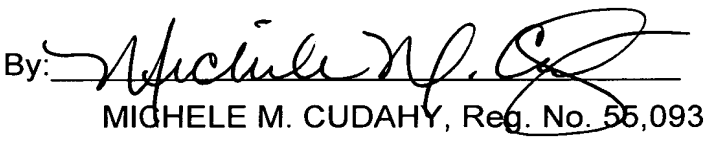
By: 

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